REMARKS

Claims 25-48 and new claim 49 are pending in this application for the Examiner's review and consideration. New claim 49 is fully supported by the specification (*See*, specification, ¶ [0013] and [0028]). No new matter is added by this new claim so that its entry at this time is warranted. Applicants have not canceled withdrawn method claims 38-48. The Manual of Patent Examining Procedure ("MPEP") states that when:

> The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder .

(*See*, MPEP ¶ 806.05(h) and Form paragraph 8.21.04). Accordingly, because process of use claims 38-48 depend from independent product claim 25, Applicants respectfully request that these process of use claims be rejoined if product claim 25 is found allowable.

Applicant appreciates the courtesy extended to Applicant's attorney, Paul E. Dietze, in a telephonic interview on December 11, 2007. The remarks provided below are in substantial accordance with and follow up on the discussions held during the interview.

THE REJECTION UNDER 35 U.S.C. § 103(A)

The Rejection of Claims 25-35 and 37 as Obvious Over U.S. Patent No. 4,311,857 in View of Design of Prodrugs

Claims 25-35 and 37 were rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. patent no. 4,311,857 to Nagabhushan ("Nagabhushan") in view "*Design of Prodrugs*" edited by H. Bundgaard ("Bundgaard") for the reasons set forth on pages 3-5 of the Office Action. Applicant respectfully traverses. Specifically, the Examiner asserts that Nagabhushan teaches pharmaceutical compositions comprising D-(threo)-1-p-methylsulfonylphenyl-2-chloroacetamido-3-fluoro-1-propanol (florfenicol) together with a pharmaceutical carrier. The Examiner also asserts that Nagabhushan discloses injectable formulations, that ester derivatives are also antibacterially active, and that propylene glycol is compatible with florfenicol. The Examiner acknowledges that Nagabhushan does not expressly teach combinations of florfenicol esters in a single formulation or the specific concentration of florfenicol. The Examiner then

asserts that Bundgaard teaches that ester formation is an effective means to increase the aqueous solubility of drugs that contain a hydroxyl group to provide a prodrug that is suitable for parenteral administration. Therefore, the Examiner asserts

> It would have been obvious to one of ordinary skill in the art to employ ester derivatives of florfenicol such as florfenicol butyrate, florfenicol propionate, and florfenicol acetate etc. taught by Nagabhushan in a single formulation for parenteral administration because ester prodrugs taught by Nagabhushan have beneficial effects in parenteral formulation because they increase the aqueous solubility of drugs containing hydroxyl groups such as florfenicol and this is a well known and recognized effective means of preparing parenteral formulation as taught by Bundgaard.

The Examiner asserts that one would be motivated to make such a modification in order to achieve the active florfenicol *in vivo* by hydrolysis of the prodrug of florfenicol. The Examiner also asserts that to provide more than one ester in a single formulation is obvious because each of the esters have antibacterial activity. Applicant respectfully traverses.

As the Examiner is aware, in order to render claims obvious under 35 U.S.C. § 103(a), the prior art must disclose or suggest every limitation of the claimed invention and provide the person of skill in the art with a reasonable expectation that the invention will work for its intended purpose. *KSR International Co. v. Teleflex Inc. et al.*, 127 S.Ct. 1727 at 1739-41 (2007). Applicant respectfully submits that the prior art cited by the Examiner does not render the claims obvious because the cited art does not disclose or suggest each and every feature of the claims or provide a reasonable expectation that the invention will work for its intended purpose.

Independent Claim 25 and Claims Dependent Therefrom

Although Nagabhushan discloses esters of florfenicol there is no disclosure or suggestion in Nagabhushan to make a formulation that comprises *both* a first ester prodrug of florfenicol and a second ester prodrug of florfenicol, as recited in independent claim 25. Although one of ordinary skill in the art formulating a composition for administering florfenicol might chose to formulate the composition using a prodrug of florfenicol, which could be an ester of florfenicol, one of ordinary skill would not chose to use a mixture of esters absent some motivation to do so. Rather, absent some motivation to do otherwise, one of ordinary skill choosing to use an ester prodrug of florfenicol would select a single ester. Although Nagabhushan discloses esters of

florfenicol and Bundgaard discloses that prodrugs are used to increase aqueous solubility, neither reference discloses or suggests a formulation that comprises *both* a first ester prodrug of florfenicol and a second ester prodrug of florfenicol, as recited in independent claim 25. The mere disclosure of esters of florfenicol is not a disclosure to and does not provide motivation to combine two different esters in a single formulation, much less esters with different release rates.

The composition claimed in claim 25, which includes the combination of a first ester prodrug of florfenicol and a second ester prodrug of florfenicol formulated as a composition for administration to a mammal by injection, however, has unexpected advantages that are not disclosed or suggested in either Nagabhushan or Bundgaard. Specifically, the claimed composition advantageously provides a composition that, when administered to the mammal, allows for an "initial burst" followed by a slower more sustained release to provide a better pharmacokinetic profile (*See*, Specification, ¶ [0028] - [0029], [0036], and Example 10, ¶ [0058]). The claimed composition is a therapeutically more effective product and a safer composition compared to a composition containing only a first ester prodrug of florfenicol. Thus, the claimed compositions, by providing a slower more sustained release, actually go away from the teaching of Bundgaard that the esters should "convert rapidly *in vivo* to the active parent drug by hydrolysis" (*See*, Office Action, page 4, second full paragraph). For the above reasons, Applicant respectfully submits that Nagabhushan and Bundgaard do not render independent claim 25 and claims dependent therefrom obvious.

Clearly, Nagabhushan and Bundgaard, either individually or in combination, do not render obvious dependent claim 29, which recites that the "first ester prodrug of florfenicol and the second ester prodrug of florfenicol are selected from the group consisting of florfenicol acetate, florfenicol propionate, florfenicol butyrate, florfenicol pentanoate, florfenicol hexanoate, florfenicol heptanoate, florfenicol octanoate, florfenicol nanoate, florfenicol decanoate, florfenicol undecanoate, florfenicol dodecanoate, and florfenicol phthalate." As acknowledged by the Examiner, the motivation for one of ordinary skill in the art to select an ester prodrug is to increase the water solubility of the prodrug (*See*, Office Action, page 4, second full paragraph). Indeed, the Examiner cites Bundgaard for teaching "that ester formation has long been recognized as an effective means of increasing the aqueous solubility of drugs containing a hydroxyl group." Applicant notes, however, that each of the esters recited in dependent claim 29

are *less* soluble in water than florfenicol (*See*, specification, ¶ [0028]), *i.e.*, making the ester decreases the water solubility. Thus, one of ordinary skill in the art would not be motivated to select one of the esters recited in claim 29 because it goes against the teaching of Bundgaard. Similarly, Nagabhushan discloses that esters having increased solubility in water are preferred (*See*, Nagabhushan, column 5, lines 15-25). If anything, one of ordinary skill in the art, aware of Nagabhushan and Bundgaard, would select a single ester (for the reasons set forth above) and would select one of the esters, disclosed in Bundgaard and/or Nagabhushan, that lead to better solubility in water (such as a hemisuccinate, phosphate, dialkylaminoacetate or amino acid ester (*See*, Bundgaard, page 8 and Nagabhushan, column 5, lines 15-25)) rather than one of the esters recited in claim 29 that have *less* solubility in water. Applicants respectfully submit that Nagabhushan and Bundgaard do not render claim 29 and claims dependent therefrom obvious for this additional reason.

Similarly, Nagabhushan and Bundgaard, either individually or in combination, do not render obvious dependent claim 31, which recites "the composition forms a drug depot when injected into a mammal." There is absolutely no disclosure or suggestion in Nagabhushan and Bundgaard of a composition that provides a depot when injected into a mammal. Depot formation is the result of selecting ester prodrugs of florfenicol that are less soluble than florfenicol. As discussed above, Nagabhushan and Bundgaard teach making prodrugs that increase, not decrease, solubility in water (*See*, Office Action, page 4, second full paragraph). Thus, the recitation in claim 31 that the composition forms a drug depot when injected into the mammal goes against the teaching of Nagabhushan and Bundgaard. Thus, Nagabhushan and Bundgaard clearly teach away from the recitation in dependent claim 31 of a "drug depot." Applicants respectfully submit that Nagabhushan and Bundgaard do not render dependent claim 31 obvious for this additional reason.

Applicant respectfully submits that the rejection of independent claim 25 and claims dependent therefrom as being obvious over Nagabhushan and Bundgaard involves hindsight reconstruction of Applicant's invention. The Examiner is using Applicant's disclosure as a blueprint to combine selected parts of Nagabhushan and Bundgaard, when there is no motivation to do so, and, in fact, a teaching not to do so. It is well settled that hindsight cannot be used to reject a claim as obvious. *In re Sernaker,* 702 F.2d 989, 994 (Fed. Cir. 1983); *In re Rinehart,*

531 F.2d 1048 (CCPA 1976); *In re Imperato,* 486 F.2d 585 (CCPA 1973); *In re Adams,* 356 F.2d 998 (CCPA 1966); *In re Anita Dembiczak,* 75 F.3d 994, 999 (Fed. Cir. 1999); *C.R. Bard Inc. v. M3 Systems, Inc.,* 157 F.3d 1340, 1352 (Fed. Cir. 1998) citing *Fromson v. Advance Offset Plate, Inc.,* 755 F.2d 1549, 1556 (Fed. Cir. 1985) (holding the prior art must suggest to one of ordinary skill in the art the desirability of the claimed combination).

For the reasons set forth above, Applicant respectfully submits that Nagabhushan and Bundgaard do not render independent claim 25 and claims dependent therefrom obvious.

New claim 49 is also patentable over Nagabhushan and Bundgaard for the same reasons that claim 25 is patentable. Furthermore, claim 49 includes the additional features that that the composition is formulated for administration to a mammal by injection and that the composition forms a drug depot when injected into the mammal. As discussed above, there is absolutely no disclosure or suggestion in Nagabhushan and Bundgaard of a composition that provides a depot when injected into a mammal. Depot formation is the result of selecting ester produgs of florfenicol that are less soluble than florfenicol. Nagabhushan and Bundgaard teach making prodrugs that to increase, not decrease, solubility in water. Thus, the recitation in claim 49 that the composition forms a drug depot when injected into the mammal goes against the teaching of Nagabhushan and Bundgaard. New claim 49 also recites the additional feature that the release rate of the first ester prodrug of florfenicol is different from the release rate of the second ester prodrug of florfenicol. As discussed above, neither Nagabhushan nor Bundgaard, individually or in combination, disclose or suggest a composition that contains both a first ester prodrug of florfenicol and a second ester prodrug of florfenicol, much less the feature that the release rate of the first ester prodrug of florfenicol and the second ester prodrug of florfenicol are different. Neither Nagabhushan nor Bundgaard even recognize that release rate can be effected by varying the ester. Applicant respectfully submits that neither Nagabhushan nor Bundgaard, either individually or in combination, render new claim 49 obvious.

Independent Claim 34 and Claims Dependent Therefrom

Nagabhushan and Bundgaard also do not render independent claim 34 obvious. There is no disclosure in Nagabhushan and Bundgaard to prepare a pharmaceutical composition comprising florfenicol butyrate. Although, Nagabhushan discloses a laundry list of florfenicol

esters (*See*, Nagabhushan, column 4, line 41 to column 5, line 25), there is no disclosure or motivation to select the butyrate ester. The Examiner asserts, however, that this lack of disclosure and motivation is "not found persuasive because the advantages of prodrug esters are long recognized as an effective means of increasing the aqueous solubility of drugs containing a hydroxyl group in view of Bundgaard" (*See*, Office Action, page 7). Applicant respectfully disagrees. First, as acknowledged by the Examiner, Bundgaard motivates one to select an ester prodrug to increase the aqueous solubility of the drug. However, as discussed above, florfenicol butyrate is *less* soluble in water than florfenicol (*See*, specification, ¶ [0028]). Thus, one of ordinary skill in the art, aware of the teaching of Bundgaard, would not be motivated to select florfenicol butyrate because it has less solubility in water than florfenicol and goes against the teaching of Bundgaard. If anything, one of ordinary skill in the art, aware of Nagabhushan and Bundgaard, would select one of the esters disclosed in Bundgaard that lead to better solubility in water (such as a hemisuccinate, phosphate, dialkylaminoacetate or amino acid ester (*See*, Bundgaard, page 8)) and not an ester that has *lower* aqueous solubility, much less the specific ester florfenicol butyrate.

Indeed, even if the prior art teaching was not limited to selecting prodrugs with increased water solubility, neither Nagabhushan nor Bundgaard provide any motivation to select the specifically claimed butyrate ester of florfenicol. Applicant, however, has unexpectedly discovered, as set forth in the previous response dated July 27, 2007, that injectable compositions containing florfenicol butyrate are superior to compositions that contain florfenicol or other prodrugs of florfenicol. In particular, when administered to a cat, florfenicol butyrate compositions are superior at providing an effective level of florfenicol in the serum while reducing toxicity. Unlike other prodrugs of florfenicol that were studied, when florfenicol butyrate is administered to a cat and samples of the cat's serum analyzed over time, there is detected in the serum effective levels of florfenicol but undetectable levels of the prodrug (*i.e.*, the florfenicol butyrate). Without wishing to be bound by theory, Applicant believes that this is due to florfenicol butyrate having a unique release rate and metabolism rate by esterases so that when a composition comprising florfenicol butyrate and a pharmaceutically acceptable solvent is administered to a cat it provides a serum level of florfenicol that is unexpectedly safe and effective. The superiority of florfenicol butyrate compared to florfenicol was clearly described in the response dated July 27, 2007 (*See*, discussion in the previous response dated July 27, 2007

at pages 9-11) and, therefore, is not repeated in detail herein.

The Examiner, however, asserts that "Applicants surprising and unexpected result of florfenicol butyrate having better pharmacological profile than Nuflor is an expected result in view of Bundgaard who teaches that ester formation has long been recognized as an effective means of increasing the aqueous solubility of drugs containing a hydroxyl group" (*See*, Office Action, paragraph bridging pages 7-8). Contrary to the Examiner's assertion, the discovery that florfenicol butyrate has a better pharmacological profile than Nuflor is **not** an expected result. There is absolutely no disclosure in Bundgaard, or Nagabhushan, that the butyrate ester would have an advantageous pharmacological profile. Bundgaard simply discloses that ester prodrugs (specifically, hemisuccinate, phosphate, dialkylaminoacetate or amino acid ester (*See*, Bundgaard, page 8)) can be used to increase the aqueous solubility of drugs that have a hydroxyl group. There is, however, absolutely no disclosure in Bundgaard that selecting an ester as a prodrug, much less a butyrate ester prodrug that has *less* solubility in water than the drug, could be used to provide a pharmacological profile that is superior to the pharmacological profile of the drug itself or other ester prodrugs. Similarly, Nagabhushan is completely silent concerning the pharmacological profile of prodrugs of florfenicol.

As further evidence that florfenicol butyrate is superior to florfenicol and other esters of florfenicol, Applicants submit herewith another Declaration under 37 C.F.R. § 1.132, by Dr. Murthy, one of the inventors, ("Second Declaration") describing the results of a study wherein calves were administered either florfenicol, florfenicol acetate, florfenicol butyrate, or florfenicol hexanoate. The results described in the Second Declaration clearly show that administering florfenicol butyrate results in a pharmacokinetic profile for the serum florfenicol concentration that is superior to florfenicol, florfenicol acetate, or florfenicol hexanoate (*See*, Second Declaration at ¶¶ 8-10). Specifically, administering the florfenicol butyrate composition provided a therapeutically effective serum concentration of florfenicol for a longer period of time than any of the other compositions (*See*, Second Declaration at ¶ 8). The florfenicol butyrate composition was the only composition that provided a therapeutically effective serum florfenicol concentration for a period of time longer than 36 hours (*See*, Second Declaration at ¶ 8). Also, administering the florfenicol butyrate composition avoided a rapid increase in the serum concentration of florfenicol (*i.e.*, "spike") that is associated with administering florfenicol (*See*,

Second Declaration at ¶ 9). The results of the experiments described in the Second Declaration clearly show that administering florfenicol butyrate results in a a pharmacokinetic profile of serum florfenicol concentration that is superior to the pharmacokinetic profile obtained when florfenicol (*i.e.*, Nufluor®) or other florfenicol esters are administered (*See*, Second Declaration at ¶ 10). Thus, administering florfenicol butyrate advantageously avoids having to administer multiple injections, which is safer, simpler, less stressful for the animal, and more cost effective (*See*, Second Declaration at ¶ 8). Moreover, the beneficial pharmacokinetic profile is not predictable and appears to be the result of a combination of unique properties of florfenicol butyrate (*See*, Second Declaration at ¶ 10).

Applicant respectfully submits, for the reasons set forth above, that independent claim 34 and claims dependent therefrom are not obvious in view of Nagabhushan and Bundgaard.

The Rejection of Claim 36 as Obvious Over U.S. Patent No. 4,311,857 in View of Design of Prodrugs and U.S. Published Application No. US 2004/0198704

Claim 36 was rejected under 35 U.S.C. § 103(a) as unpatentable over Nagabhushan in view Bundgaard and further in view of US 2004/0198704 ("Schuster") for the reasons set forth on pages 5-7 of the Office Action. Applicant respectfully traverses. The Examiner applied Nagabhushan and Bundgaard as it was applied to claims 25-35, discussed above. The Examiner then asserts that Schuster teaches formulations that include a compound selected from a genus of compounds that include florfenicol derivatives that encompass florfenicol butyrate; that the compositions can be formulated with N-methyl-2-pyrrolidone, 2-pyrrolidone, glycerol formal, propylene glycol, polyethylene glycol, ethanol, and DMSO; for treating bacterial infections; and that they can be formulated to be injectable. The Examiner then asserts that it would have been obvious to combine glycerol formal in the compositions of Nagabhushan as modified by Bundgaard.

As discussed above, Nagabhushan and Bundgaard, either individually or in combination, do not render independent claim 34 obvious. Schuster does not remedy the deficiencies in Nagabhushan and Bundgaard. The mere disclosure in Schuster that a laundry list of florfenicol esters (*See*, Schuster, ¶ [0047] - [0049]) can be formulated in a variety of solvents does not remedy the deficiencies in Nagabhushan and Bundgaard, discussed in detail above.

Accordingly, Applicants respectfully submit that Nagabhushan, Bundgaard, and Schuster, either individually or in combination, do not render claim 36 obvious. Accordingly, Applicants respectfully request that the rejection of claim 36 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

For the reasons set forth above, Applicant respectfully requests that the rejection of claims 25-37 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

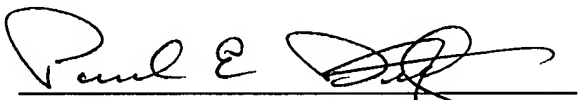
CONCLUSIONS

It is respectfully submitted that all claims are now in condition for allowance, early notice of which would be appreciated. Should the Examiner disagree, Applicant respectfully requests a telephonic or in-person interview with the undersigned attorney to discuss any remaining issues and to expedite eventual allowance of the claims.

Also submitted herewith is Petition for Extension of Time with the required fee to extend the time for responding by 1 month from January 18, 2007 to and including February 18, 2008.

A fee of $50.00 is believed to be due for the addition of one (1) claim in excess of twenty (20). Should any additional fees be required, please charge the required fees to Kenyon & Kenyon deposit account no. 11-0600.

Respectfully submitted,



Date: January 31, 2008

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